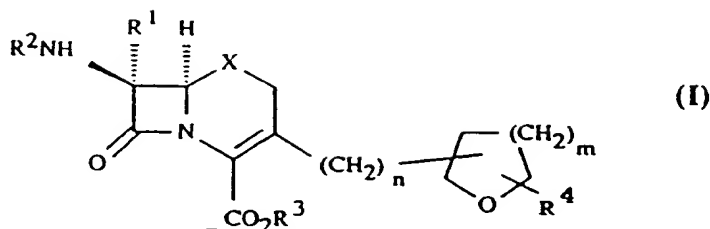


Claims

1. A compound of formula (I) or a salt thereof:



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wherein

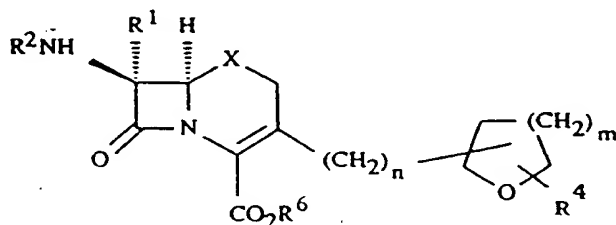
R^1 is hydrogen, methoxy or formamido;

R^2 is an acyl group;

CO_2R^3 is a carboxy group or a carboxylate anion, or R^3 is a readily removable carboxy protecting group;

R^4 represents up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R , $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alkyl), aryl and heterocyclyl, which may be the same or different and wherein any R^4 alkyl substituent is optionally substituted by any other R^4 substituent; X is S, SO, SO_2 , O or CH_2 ; m is 1 or 2; and n is 0.

2. A compound as claimed in claim 1 having the formula (Ia):



(Ia)

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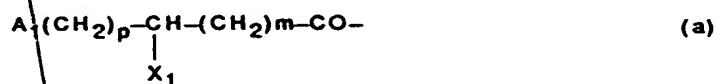
-137-

wherein R^1 , R^2 , R^4 , m , n and X are as defined with respect to formula (I) in claim 1 and the group CO_2R^6 is CO_2R^3 where CO_2R^3 is a carboxy group or a carboxylate anion, or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof.

3. A compound as claimed in claim 1 or claim 2 wherein R^1 is hydrogen.

10 4. A compound as claimed in claim 1, 2 or 3 wherein R^2 is an acyl group of formula (a) to (f):

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-138-

wherein p is 0, 1 or 2; m is 0, 1 or 2; A₁ is C₁₋₆ alkyl, substituted C₁₋₆ alkyl, C₃₋₆ cycloalkyl, cyclohexenyl, cyclohexadienyl, an aromatic or heteroaromatic group; X₁ is a hydrogen or halogen atom, a carboxylic acid, carboxylic ester, sulphonic acid, azido, tetrazolyl, hydroxy, acyloxy, amino, ureido, acylamino, heterocyclylamino, guanidino or acylureido group; A₂ is an aromatic or heteroaromatic group, a substituted alkyl group; or a substituted dithietane; X₂ is a -CH₂OCH₂-, -CH₂SCH₂- or alkylene group; X₃ is an oxygen or sulphur atom; A₃ is an aryl or heteroaryl group; and A₄ is hydrogen, C₁₋₆alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl(C₁₋₆)alkyl, C₁₋₆ alkoxycarbonyl(C₁₋₆) alkyl, C₂₋₆ alkenyl, carboxy(C₁₋₆)alkyl, C₂₋₆ alkynyl, aryl or C₁₋₆alkyl substituted by up to three aryl groups.

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5. A compound as claimed in claim 4 wherein A₁ is optionally substituted phenyl, X₁ is hydrogen or amino, A₂ is optionally substituted phenyl, X₃ is oxygen, A₃ is aminothiazolyl, aminothiadiazolyl or furyl, and R₄ is hydrogen, C₁₋₆ alkyl, or carboxy C₁₋₆ alkyl.

6. A compound as claimed in any one of claims 1 to 5 wherein CO₂R³ is carboxy or a carboxylate anion or R³ is t-butyl, 4-methoxybenzyl, diphenylmethyl, acetoxymethyl, acetoxylethyl, pivaloyloxymethyl, propan-2-yloxycarbonyloxyethyl or 2-ethoxycarbonyl-but-2-enyl.

7. A compound as claimed in any one of claims 1 to 6 wherein the cyclic ether group bonded to the 3-position of the cephalosporin nucleus is unsubstituted or unsubstituted by up to three substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkanoyloxy C₁₋₆ alkyl or C₁₋₆ alkoxy C₁₋₆ alkyl.

8. A compound as claimed in any one of claims 1 to 7 wherein m is 1.

-139-

9. A compound as claimed in any one of claims 1 to 8 wherein the cyclic ether group is a tetrahydrofuran-2-yl or a tetrahydropyran-2-yl group.
- 5 10. Sodium (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
11. Pivaloyloxymethyl (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
- 10 12. Sodium (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydropyran-2-yl]-15 ceph-3-em-4-carboxylate.
13. Pivaloyloxymethyl (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydropyran-2-yl]ceph-3-em-4-carboxylate.
- 20 14. (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-hydroxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylic acid.
- 25 15. Sodium (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
- 30 16. Pivaloyloxymethyl (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

-140-

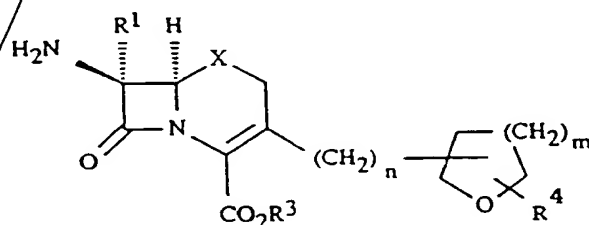
17. Sodium (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(R)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
- 5 18. Pivaloyloxymethyl (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(R)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
19. Diphenylmethyl (6R, 7R)-7-phenylacetamido-3-[(RS)-10 tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
20. Sodium (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido-3-[(RS)-tetrahydrofuran-3-yl]ceph-3-em-4-carboxylate.
- 15 21. Acetoxymethyl (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylate.
- 20 22. Sodium (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(5-methoxymethyltetrahydrofuran-2-yl)ceph-3-em-4-carboxylate
23. Sodium (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-(Z)-pent-25 2-enamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
24. Sodium (6R, 7R)-7-[2-(2-Aminothiadiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-30 em-4-carboxylate.

-141-

25. (RS)-1-Acetoxyethyl (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
- 5 26. (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-carboxymethoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylic acid disodium salt.
27. Sodium (6R, 7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)-
10 acetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
28. Sodium (1S, 6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-
15 em-4-carboxylate-1-oxide.
29. Sodium 7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(tetrahydrofuran-2-yl)-1-carba-1-dethia-
ceph-3-em-4-carboxylate.
- 20 30. Sodium (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxy-iminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate-1,1-dioxide.
- 25 31. (RS)-1-(Propan-2-yl)oxycarbonyloxyethyl (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
32. Sodium (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-
30 methoxyiminoacetamido]-3-[(5R, 2SR)-5-methyltetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

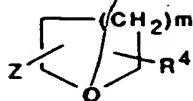
-142-

33. Sodium (6R, 7R)-7-[2-(furan-2-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
- 5 34. Sodium (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-5,5-dimethyltetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
35. Sodium (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(5-methoxycarbonyltetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.
- 10 36. Sodium (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[3-methyltetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
- 15 37. 2-Ethoxycarbonyl-(Z)-but-2-enyl (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetomido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.
- 20 38. A compound of formula (I) as defined in claim 1 substantially as hereinbefore described with reference to the preparative examples.
- 25 39. A process for the preparation of a compound of formula (I) as defined in any one of claims 1 to 28 which process comprises:
- (a) treating a compound of formula (II) or a salt thereof:



(II)

-144-



(XI)

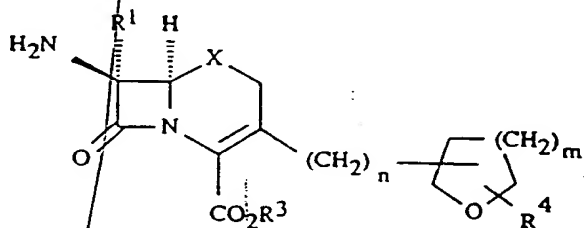
wherein Z is an organo-cuprate group and R^4 and m are as hereinbefore defined with respect to formula (I) in claim 1;

and thereafter, if necessary or desired, carrying out one of the following steps:

- i) removing any protecting groups;
- ii) converting the group CO_2R^3 to a different group CO_2R^3 ;
- iii) converting the group R^2 to a different group R^2 ;
- iv) converting the group X to a different group X;
- v) converting the product into a salt.

40. A process for the preparation of a compound of formula (I) substantially as hereinbefore described in the preparative Examples.

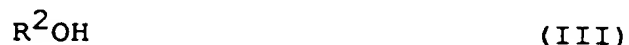
41. A compound of formula (II) or a salt thereof:



(II)

-143-

wherein R^1 , CO_2R^3 , R^4 , m , n , and X are as hereinbefore defined with respect to formula (I) in claim 1, wherein any reactive group may be protected, and wherein the amino group is optionally substituted with a group which permits -
 5 acylation to take place, with an N -acylating derivative of an acid of formula (III):

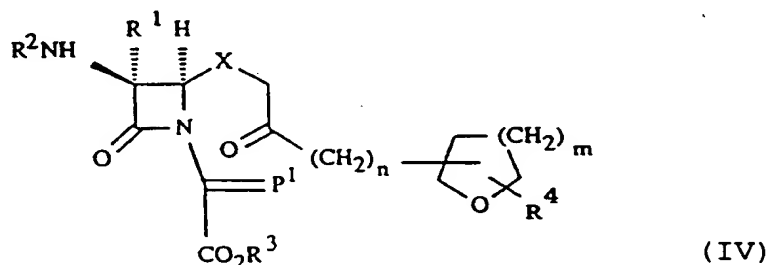


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wherein R^2 is as hereinbefore defined with respect to formula (I) in claim 1 and wherein any reactive group may be protected; or

15 (b) cyclising a compound of formula (IV):

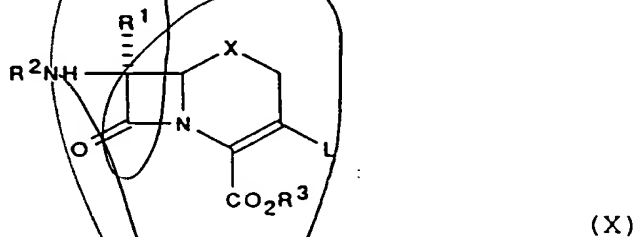
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wherein X , R^1 , R^2 , R^4 , m , n and CO_2R^3 are as hereinbefore defined with respect to formula (I) in claim 1 and P' is a
 25 phosphorus residue; or

(c) treating a compound of formula (X):

30



35 wherein R^1 , R^2 , CO_2R^3 and X are as hereinbefore defined with respect to formula (I) in claim 1, and L is a leaving group, with a compound of formula (XI):

-145-

wherein R^1 , CO_2R^3 , R^4 , X , m and n are as hereinbefore defined with respect to formula (I) in claim 1.

42. t-Butyl 6R, 7R-7-Amino-3-(tetrahydrofuran-2-yl)-
5 ceph-3-em-4-carboxylate.

43. t-Butyl (6R, 7R)-7-Amino-3-[(RS)-tetrahydropyran-
2-yl]ceph-3-em-4-carboxylate.

10 44. 4-Methoxybenzyl (6R, 7R)-7-amino-3-(tetrahydrofuran-
2-yl)ceph-3-em-4-carboxylate.

45. Pivaloyloxymethyl (6R, 7R)-7-amino-3-(tetrahydro-
furan-2-yl)ceph-3-em-4-carboxylate.

15

46. t-Butyl (6R, 7R)-7-Amino-3-[(RS)-tetrahydrofuran-3-
yl]ceph-3-em-4-carboxylate.

47. Acetoxymethyl (6R, 7R)-7-amino-3-[(S)-tetrahydro-
20 furan-2-yl]ceph-3-em-4-carboxylate.

48. 4-Methoxybenzyl (6R, 7R)-7-Amino-3-(5-methoxymethyl-
tetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

25 49. 4-Methoxybenzyl (6RS, 7SR)-7-amino-3-(tetrahydro-
furan-2-yl)-1-carba-1-dethiaceph-3-em-4-carboxylate.

50. 4-Methoxybenzyl (6R, 7R)-7-amino-3-(5-methyl-
tetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

30

51. A compound of formula (II) as defined in claim 41
substantially as hereinbefore described with reference to
the preparative Examples.

-146-

52. A pharmaceutical composition comprising a compound of formula (Ia) as defined in claim 2 or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, and a pharmaceutically acceptable carrier.

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53. A pharmaceutical composition as claimed in claim 52 further comprising a β -lactamase inhibitor.

54. A compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof as defined in claim 2, for use as a therapeutic agent.

55. A method of treating bacterial infections in humans and animals which comprises administering a therapeutically effective amount of a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, as defined in claim 2, to a human or animal.

56. The use of a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, as defined in claim 2, for the manufacture of a medicament for the treatment of bacterial infections.